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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,123	03/16/2001	Sharon Erickson	GENENT.073A2	6508

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,123	ERICKSON ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6 and 8-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 8-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment filed February 24, 2003 (Paper No. 13) is acknowledged. Claims 18, 19, 26, 36, 43 and 46-48 were amended.

Claims 1, 2, 4-6, and 8-48 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The petition to correct inventorship is acknowledged. However, the petition is insufficient for the following reasons:

The new declaration was not signed by all of the inventors (see MPEP 201.03, B. Oath or Declaration).

The petition lacks a statement by Walter A. Blattler indicating that his omission was without deceptive intent.

The petition lacks an adequate written consent by the assignee. The letter of consent present in the file contains no indication that the person signing has the authority to act on behalf of the assignee (see MPEP 201.03, D. Written Consent of Assignee).

Claim Rejections Withdrawn:

4. The objection to claim 26 for referring to Figure 1 is withdrawn in view of the amendment.

5. The rejection of claims 18, 19, 36, 43, 46, 47 and 48 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment removing the trademark "HERCEPTIN".

6. The rejection of claims 14-16, 18, 19, 35, 36, 43, and 46-48 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of applicant's persuasive arguments.

7. The rejection of claims 1, 2, 4-6, 8-17, 20-35, and 37-42 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. 6,436,931; issued Aug. 20, 2002; effective filing date Nov. 24, 1999) in view of Hudziak (U.S. 5,725,856; issued Mar. 10, 1998; effective filing date Jan. 12, 1988) is withdrawn upon further consideration of the teachings of Chari (U.S. 6,436,931).

8. The rejection of claims 1, 34, and 37 under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. 6,436,931; issued Aug. 20, 2002; effective filing date Nov. 24, 1999) in view of Hudziak (U.S. 5,725,856; issued Mar. 10, 1998; effective filing date Jan. 12, 1988) in view of Kasprzyk (Cancer Res. 52: 2771-2776; cited in the IDS) is withdrawn upon further consideration of the teachings of Chari (U.S. 6,436,931).

New Grounds of Rejections:

9. Claims 14 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is indefinite because it lacks a definition of R in the figure representing DM1.

Claim 14 is indefinite because the scope of antibodies that are antibodies having the biological characteristics of the 4D5 antibody cannot be determined. The specification provides an open definition of what biological characteristics are to be considered when comparing other antibodies that bind to Her-2 with the 4D5 antibody. Also it is not clear if all biological characteristics should be considered together or if a comparison of one biological characteristics is sufficient in deciding if an antibody is to be included within the scope of the claim.

10. Claims 1, 2, 4-6, 8-17, 20-33, and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Hudziak (U.S. Patent 5,725,856; issued Mar. 10, 1998; effective filing date Jan. 12, 1988).

Chari discloses antibody conjugates comprising one or more maytansinoids (abstract and claims; and col. 9, line 65- col. 10, line 13, lines 24-43; col. 10, line 64- col.11; line 13; lines 24-44; col. 11, line 63-col. 12, line11) and methods of use (col. 4, lines 8-14). Chari teaches specific fragments of antibodies (col. 10, lines 5-7). Chari teaches linking by a disulfide group (col. 10, lines 9-13) and other linkers (col. 10, lines 24-43).

Chari fails to teach conjugates comprising an antibody that binds to ErbB2.

However, Hudziak teaches methods treating cancer comprising administering anti ErbB2 antibodies conjugated to cytotoxic agents(col. 9, line 56 – col. 10, line15). Hudziak teaches an anti-ErbB2 antibody that is growth inhibitory antibody (col. 18 – col. 19). Hudziak teaches the 4D5 monoclonal antibody. Hudziak teaches that the antibody may be an antibody fragment (col. 10, lines 14-15). Hudziak teaches specific linkers (col. 10, lines 3-14).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Hudziak to make the claimed inventions. One would have been motivated to use the antibodies of Hudziak to make the claimed conjugates because Hudziak teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (col. 2, lines 38-54).

Applicant argues that the prior art fails to teach methods for treating cancers that respond poorly to treatment with an anti-ErbB2 antibody. This argument is not persuasive, because the art recognizes that anti-ErbB2 antibodies may be conjugated to cytotoxic moieties, where the antibody is used as targeting agents, and therefore, such conjugates would inherently be useful for the treatment of tumors that do not respond to an anti-ErbB2 antibody by itself, because the tumors would be expected to respond to the cytotoxic moiety. Furthermore, the property of failing to respond or of responding poorly to the anti-ErbB2 antibody may be a function of the epitope that the antibody binds to on ErbB2 or may be a function of the particular characteristics of the tumor (e.g., the tumor has alternative growth promoting pathways).

11. Claims 1, 2, 4-6, 8-33, 38-41, 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct.

25, 1989) in view of Carter (U.S. Patent 6,054,297; issued Apr. 25, 2000; effective filing date Aug. 21, 1992).

The claimed inventions are drawn to methods employing antibody conjugates comprising humanized anti-ErbB2 antibodies, where the humanized antibodies are humanized 4D5 antibodies. The humanized 4D5 antibodies may be any of huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8. The treatment with the maytansinoid conjugate may have an improved objective response rate, have a longer duration of response or result in increased survival compared to treatment with huMab4D5-8 alone.

Chari teaches as set forth above. Chari fails to teach conjugates comprising a humanized 4D5 antibody and any of the named humanized 4D5 antibodies (huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8).

However, Carter teaches humanized 4D5 antibodies and teaches each of the species of named species (huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8) by the disclosure of how to make these antibodies (see col. 49, line 27-col. 53-23 and col. 13, lines 20-30). Carter also teaches the humanized4D5 antibodies may be used as immunotoxins, where they are conjugated with a cytotoxic.moiety (see col. 44, line 23- col. 45, line 30).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Carter to make the claimed inventions. One would have been motivated to use the antibodies of Carter to make the claimed

conjugates because Carter teaches that ErbB2 (Her-2) is amplified or overexpressed in many human malignancies (col. 3, line56- col. 4, line 19). It would have been expected that the an conjugate comprising maytansinoid would result in an improvement over treatment with huMab4D5-8 alone because treatment with a conjugate would be effectively treatment with two anticancer agents, one the maytansinoid, and the other the humanized 4D5 antibody.

The claimed methods can be viewed as a methods drawn to administering a combination of ingredients known in the art to be useful for the same purpose, i.e. an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06).

11. Claims 1, 2, 4-14, 20-33, and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Bacus (U.S. Patent 5,514,554; issued May 7, 1996; filing date Oct. 7, 1993).

Chari teaches as set forth above in Section No. 10. Chari fails to teach conjugates comprising an anti-ErbB2 antibody.

However Bacus teaches anti-ErbB2 antibodies that are growth inhibitory, that induce cell death and that induce apoptosis (see Table I, col. 12) and teaches that such antibodies may be conjugated to cytotoxic moieties (col. 4, lines 1-14; col. 15, lines 29-45).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Baccus to make the claimed inventions. One would have been motivated to use the antibodies of Baccus in the claimed conjugates because Baccus teaches that antibodies bind to a cancer antigen that is expressed or over expressed on certain cancer types (col. 2, lines 32-35).

12. Claims 1, 2, 8-14, 20-33 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Huston (U.S. Patent 5,877,305; issued Mar. 2, 1999; effective filing date Feb. 6, 1992).

Chari teaches as set forth above in Section No. 10. Chari fails to teach conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments).

However, Huston teaches single-chain Fv comprising a binding site that binds to ErbB2 and methods of treatment of cancer comprising linking the single-chain Fv to a therapeutic agent, which is an agent that has the ability to limit the proliferation of a tumor cell (col. 1, lines 25-26; col. 5, lines 11-23; col. 8, lines 25-34).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of Huston to make the claimed inventions. One would have been motivated to use the single-chain Fv of Huston because it binds to a cancer antigen (see Huston, col. 2, lines 1-9).

13. Claims 1, 2, 8-14, 22-33, and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of King (U.S. Patent 5,747,261; issued May. 5, 1998; effective filing date Mar. 5, 1986).

Chari teaches as set forth above in Section No. 10. Chari fails to teach conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments).

However, King teaches methods for treating cancer that express high levels of ErbB2 (mac117) comprising the administration of antibodies that bind the ErbB2, where the antibody is linked to one or more agents that will cause injury to cells for the purpose of directing the toxic agent to the cancer cells that over express ErbB2 (see col. 16, line 61 – col. 17 line 18).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the teachings of Chari and of King to make the claimed inventions. One would have been motivated to use the antibodies of King to make the claimed inventions because King teaches that one would use such antibodies for the treatment of tumors that overexpress the antigen (col. 15, lines 54-60).

14. Claims 1, 34, 37, 42, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in combination with Hudziak (supra), Bacus (supra), Huston (supra) or King (supra) and further in view of Greene I (U.S. Patent 5,824,311; issued (Oct. 20, 1998; effective filing date Aug. 27, 1990).

Claims 1, 34, 37, 41, 44 and 45 are drawn to methods of treatment comprising the administration of combinations of antibodies that bind to ErbB2, where at least one of the anti-ErbB2 antibodies is conjugated to a maytansinoid, or both antibodies may be conjugated (claims 44, any toxin; and 45, conjugated to maytansinoid).

Chari fails to teach methods using combinations of at least two antibodies. Hudziak, Bacus, Huston or King fail to teach methods comprising the administration of a combination of two antibodies. However, Green teaches that combinations of anti-ErbB2 (p185) antibodies may be used in methods of treatment, because combinations of anti-ErbB2 antibodies often have a synergistic effect when used together (see abstract; col. 3, line 65- col. 4, line 9). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed inventions comprising the administration of combinations of antibodies, because the combination of Chari with either of Bacus, Huston or King provides a maytansinoid conjugate of an ErbB2 antibody, and the further combination with Greene I provides motivation to administer a second anti-ErbB2 antibody.

15. Claims 1, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in view of Greene II (U.S. Patent 5,705,157; issued Jan. 6, 1998; effective filing date Jul. 27, 1989).

Claims 1, and 37 are drawn to methods of treatment comprising the administration of combinations of antibodies, where at least one of the anti-ErbB2 antibodies is conjugated to a maytansinoid, and the second binds any ErbB receptor.

Chari fails to teach methods using combinations of at least two antibodies. However, Greene II teaches methods using combinations of antibodies, where one binds ErbB2 and one binds EGFR (ErbB1)) (see col. 3, lines 3-50). The antibodies may be conjugated to a therapeutic molecule that is an anticancer drug (col. 5, lines 53-58). Greene II teaches that some tumors express both ErbB2 and ErbB1 receptors, and methods of targeting both receptors produce a synergistic effect in comparison to methods where only one type of receptor is targeted (see col. 3, lines 3-17, and lines 51-56). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed inventions comprising the administration of combinations of antibodies, where one of the antibodies binds ErbB2 and one binds to EGFR.

15. Claims 1, 34-36 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (U.S. Patent 5,208,020; issued May 4, 1993; effective filing date Oct. 25, 1989) in combination with Hudziak (supra), Bacus (supra), Huston (supra) or King (supra); in view of Greene I (U.S. Patent 5,824,311; issued (Oct. 20, 1998; effective filing date Aug. 27, 1990) and further in view of Sliwkowski (Sliwkowski, M.X. et al., J. Biol. Chem., 269: 14661-14665, 1994) or Carter (supra).

Claims 1, 34-36, 42-45 are drawn to methods comprising using a combination of antibodies, where the second anti-ErbB2 antibody is 2C4 or is huMab4D5-8. The combination of Chari with any of Hudziak (supra), Bacus (supra), Huston (supra) or King (supra) and with Greene I fails to teach the use of a second antibody that is 2C4 or huMab4D5-8. However, both antibodies are known in the art, and the art teaches some of their biological functions.

Sliwkowski teaches that 2C4 may be used to inhibit the binding of heregulin to ErbB3 (page 14663, 1st col.) and Carter teaches that huMab4D5-8 acts to recruit immune effector cells to a tumor (col. 54, lines 38-46). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a method comprising the use of a second anti-ErbB2 antibody, where the second antibody was 2C4 or huMab4D5, because the prior art teaches that 2C4 is useful for inhibiting the action of heregulin on tumor cells, and because huMab4D5 recruits immune effector cells.

15. Claims 1, 4-6, 8-19, 22-25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwasa (U.S. Patent 5,217,713; issued Jun. 8, 1993; effective filing date Dec. 27, 1989) in combination with, Carter (supra), Hudziak (supra), Bacus (supra), Huston (supra) or King (supra).

Iwasa teaches an immunocomplex that comprises a bispecific antibody that binds to a tumor antigen and binds to a maytansinoid (ansamitocin; see col. 4, lines 1-30; claim 1), thus targeting a maytansinoid to a tumor. Iwasa fails to teach that the immunocomplex binds to a tumor antigen that is ErbB2. However, Carter, Hudziak, Bacus, Huston or King teach that ErbB2 is a tumor antigen that is useful for targeting. Further more, Carter, Hudziak, Bacus, Huston or King each teach antibodies from which the binding portion for the tumor antigen of Iwasa may be derived. In view of the fact that the specification fails to provide a definition of the term "conjugate" and in interpreting the claims broadly, the combination of Iwasa and any of Carter, Hudziak, Bacus, Huston or King may be used to make the claimed conjugates. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time

the invention was made to have made the bispecific antibody of Iwasa so that it bound to ErbB2 and could be used to target a maytansinoid to a tumor that expressed ErbB2.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
June 2, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600